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SELECTED ASPECTS OF TRIAZOLAM IN RELATION TO AVIATOR PERFORMANCE IN NAVAL FLIGHT OPERATIONS

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Benzodiazepines often are used for the management of insomnia and anxiety. Operationally they are likely to be used to phase-shift circadian rhythm. This class of drugs enhances the tendency of (GABA) to decrease neuronal firing in brain centers associated with sleep. Triazolam, like other benzodiazepines, causes impairment of various (CNS) functions, but due to its short half-life, most (but not all) CNS impairments are absent by morning. Nonetheless, this review recommends exploring the possible greater value of the newer generation of short-acting benzodiazepines and discourages further consideration of triazolam for operational consideration, because of possible adverse effects on memory and the possible narrow margin of safety. Keywords:

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SUMMARY PAGE

THE PROBLEM

The literature on the sedative-hypnotic triazolam (Halcion) is briefly reviewed. Selected effects of the drug on performance and memory, as well as reported paradoxical or untoward side effects, are discussed with relevance to possible use as a sleep aid for pilots participating in naval flight operations.

FINDINGS

Results of clinical testing indicate that up to 0.25 mg, p.o., triazolam can be taken with little or no residual performance or memory effects, provided the individual does not have to perform (including preflight brief) within 9 h of administration.

RECOMMENDATIONS

While triazolam has been thoroughly tested and widely employed in the civilian populace, this review suggests exploring the possible greater value of the newer generation of short-acting benzodiazepines and briefly mentions the use of the benzodiazepine antagonists.

INTRODUCTION

Benzodiazepines have been employed since the late 1950s for the management of insomnia and anxiety. This class of drugs acts on gamma-aminobutyrate (GABA) mediated neuronal pathways in the cerebral cortex, enhancing the tendency of GABA to decrease neuronal firing in brain centers associated with sleep and anxiety (1).

The benzodiazepines as a class also may produce central nervous system (CNS) depression, expressed as headache, dizziness, and/or hangover. To minimize residual effects, several short duration benzodiazepines have been developed: temazepam, flurazepam, triazolam, lorazepam, brotizolam, midazolam, and so forth.

The short-acting nature of these agents is important in patients with insomnia whose occupations require next-day use of fine motor skills and/or rapid and reliable cognitive processes. Such a condition may exist for some naval aviators prior to special flight operations and/or selected combat situations (2) involving irregular hours.

DRUG REVIEW

PHARMACOLOGY OF TRIAZOLAM

Triazolam is a triazolo-benzodiazepine developed in the mid-1970s. Pharmacokinetic studies in man have indicated that the drug has a relatively short time-to-peak (1.3 h), short half-life (1.5-5 h) and short elimination time (2.2-3.7 h). The only active metabolite is the short-lived alpha-hydroxytriazolam; the drug and its metabolites are excreted as glucuronide conjugates (3-5).

Triazolam has been shown to be an effective hypnotic agent, specifically, at doses of 0.25 to 0.5 mg. It produces a 10 to 60% decrease in time-to-sleep onset with an approximate 25% increase in drowsy sleep, as measured by electroencephalogram (EEG). Triazolam also increases total sleep time (12 to 25%). Rapid Eye Movement (REM) sleep also appears to be shifted. The subjective assessment of sleep is reported to be significantly better than placebo (6-12).

RESIDUAL PERFORMANCE EFFECTS

Triazolam, like other benzodiazepines, causes impairment of various CNS functions, unrelated to its sleep and anti-anxiety effects. However, due to its short half-life, most (but not all) performance effects are absent by morning, provided the dosage is 0.25 mg or less. Specifically, subjects who were given tests measuring visuomotor skills (e.g., typing, card sorting, pursuit rotor) scored lower after taking triazolam than placebo controls. These effects lasted for 5 h after subjects received 0.25 mg, and 9 h after 0.5 mg. The smaller dose of triazolam provided a performance-effect time that should well have passed, if sleep was not interrupted. Subjects continued to display normal test responses for up to 21 h (7,12,13).

Speech intelligibility was also affected by triazolam, but at much larger doses (1-2 mg) and a for shorter period of time, only during the initial 2 h (14). Similarly, subjects performing reaction time tests have shown latency increases compared to controls at 3.5 h, but not at 8 h or up to 21 h after dosing with 0.5 mg triazolam (12). Triazolam also has been reported to produce mild loss of balance for 3.5 h after a dose of 0.25 mg and for 5 h after 0.5 mg (15,16).

EFFECTS ON MEMORY

Reports of triazolam producing profound anterograde amnesia and memory loss were published soon after the drug was released (17,18). Clinical results indicate that triazolam does cause anterograde amnesia, i.e., less recall of events after taking the drug (12,19). Triazolam-induced memory loss has been reported to occur up to 8 h post-drug administration (20). Roth et al. (8) reported that triazolam-induced memory loss was dose-dependent with an approximate 10% reduction occurring in response to a 0.25 mg dose. Significant impairments in the memory span for digits and telephone number recall were reported for subjects who received 0.25 mg triazolam (8).

Memory recall for such items as phone numbers, words, and cognitive tasks were all equally affected above placebo controls (12,19). Roehrs et al. (21) found that the failure in memory recall after initial administration of drug was due to an attenuation of memory consolidation at the time of information presentation, rather than failure of retrieval. It is questionable whether such changes in memory processing would interfere with a pilot's performance during preflight briefing, inflight instructions, and so forth. Furthermore, since certain stressors are known to degrade memory, triazolam-induced amnestic effects may change under the strain of actual or anticipated combat.

OVERT SIDE EFFECTS

Initial safety evaluation of triazolam indicated the drug produced side effects of residual drowsiness, headache, dizziness, nervousness, and dry mouth in less than 5% of subjects tested (22). A later study (11) rated the side effects from mild (50%) to moderate (40%) to severe (10%). However, in 1979, van der Kroef published a letter in the Lancet (23) describing a "cluster syndrome" of depression, severe anxiety, suicidal ideations, paranoia, hyperacousis, and paresthesias in 25 insomniacs he was treating. Thereafter, the government of the Netherlands reportedly received up to 600 additional reports of one or more of the "cluster" symptoms from the use of triazolam. These reports were predominantly anecdotal, without controls, and with other possible sources of symptoms (e.g., withdrawal from other CNS agents, possible overdose, interactions with other drugs, and the patient's underlying psychopathology). As a result, these case reports received considerable criticism from the scientific community (24-26).

Van der Kroef's letter and the ensuing controversy resulted in a temporary ban of the drug in the Netherlands and prompted further studies. The results of 45 controlled clinical trials involving 5400 patients indicated subjective complaints of CNS depression (drowsiness, dizziness, fatigue, lightheadness) in 19.5% of patients receiving 0.5 mg triazolam,

14.2% receiving 0.25 mg, and 6.4% receiving placebo. No other systemic complaints were reported (27). Similarly, a monitored release of triazolam in Great Britain to 3000 patients produced no reports of "cluster syndrome" with an overall incidence of side effects of 12.2% (28). Nonetheless, triazolam appears to "have a narrow margin of safety in that serious behavioral symptoms have been reported even with a 1-mg dose" (29), which suggests an increased likelihood of a serious behavioral reaction occurring in response to the 0.25-mg dose.

DISCUSSION

Naval flight operations at sea are demanding and dangerous for all personnel involved, but are especially hazardous for the pilots. High levels of skill are required of pilots in aircraft carrier operations, as well as in many aspects of the various flight missions.

Lack of proper sleep could result in a reduction of requisite skills (30). The ideal sleep-inducing agent should help induce and maintain adequate sleep yet have no lasting effects on performance or mental health. Triazolam, given under the proper conditions, may meet these criteria. These conditions include: (1) dosage of 0.125 to 0.25 mg p.o., and (2) timing of the dose such that personnel do not fly for at least 9 h post-administration. These conditions may limit triazolam's value in scenarios where an unexpected or immediate response by aviators may be required.

In time, some of the limitations of using hypnotics may be decreased with the use of newer generation short-duration benzodiazepines (31). In fact, early studies (19, 32-36) on the performance effects of these drugs indicate they may be superior to the temazepam-triazolam generation compounds. The use of benzodiazepine antagonists such as RO15-1788 (37) or stimulants such as caffeine (38) or other amphetamines or amphetamine-like compounds may be useful in counteracting the benzodiazepine-induced effects should an emergency situation intervene.

CONCLUSIONS/RECOMMENDATIONS

This review recommends careful consideration and close patient evaluation if triazolam is used operationally because of the possible adverse effects on memory and the possible narrow margin of safety. In conclusion, it also suggests exploring the possible greater value of the newer generation short-acting benzodiazepines.

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